Case Report

An unusual presentation of a usual disorder: Van Wyk-Grumbach syndrome

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ABSTRACT

Van Wyk-Grumbach syndrome (VWGS) is characterized by juvenile hypothyroidism, delayed bone age, and isosexual precocious puberty. A 10.7-year-old girl presented with premature menarche and isosexual precocity. She had delayed bone age and multicystic ovaries. High circulating levels of TSH with prepubertal LH confirmed the diagnosis of VWGS. Tendency to manifest sexual precocity in VWGS may be directly related to the severity of the TSH elevation. High circulating levels of TSH acting directly on FSH receptors are the actual mediators of precocity.

Key words: Hypothyroidism, precocious puberty, Van Wyk–Grumbach syndrome

Introduction

The gonadotropin releasing hormone (GnRH)-dependent activation of the hypothalamic-pituitary-gonadal axis leads to central precocious puberty (CPP). The extrapituitary secretion of gonadotropins or secretion of gonadal steroids independent of pulsatile GnRH stimulation may lead to pseudoprecocious puberty, or GnRH-independent sexual precocity.[1]

Incomplete isosexual precocity is a consequence of premature increased sex hormone secretion, iatrogenic exposure of gonadal steroids, McCune–Albright syndrome, juvenile hypothyroidism in either sex, and, in boys, rarely hCG- or LH-secreting tumors.

Van Wyk-Grumbach syndrome (VWGS) is characterized by juvenile hypothyroidism, delayed bone age, and isosexual precocious puberty with reversal to a prepubertal state following thyroid hormone replacement therapy.[2]

We report a girl with long-standing, untreated hypothyroidism who presented with precocious puberty.

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Case Report

A girl aged 10 years and 9 months presented with progressive breast enlargement and menarche at 7 years of age. She had been having regular menstrual cycles with average flow. She was born of nonconsanguineous marriage at full-term, normal vaginal delivery, and was first in the birth order. Her birth weight was 2.25 kg and she had normal milestones of development.

There was no history of headache, vomiting, visual symptoms, and gelastic episodes. Her appetite was normal and she did not have excessive somnolence, cold intolerance, or constipation. Her scholastic performance continued to be average.

Her height was 114 cm (<3rd centile, target height of 165.2 cm) and weight was 25 kg. Her pulse rate was 68/min and blood pressure 98/60 mmHg. She had pallor, dry scaly skin, and depressed nasal bridge. There was no goiter. As per

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Tanner's staging, her sexual maturation score was B 4 and P3 for breast and pubic hair, respectively, and axillary hair were present. Her IQ was 76 (low average) with a verbal IQ of 73 and performance IQ of 78. Visual acuity and fields were normal.

She had normocytic normochromic anemia with a hemoglobin level of 9.8 g/dl (normal 12–14 g/dl). Hormonal investigations revealed TSH > 150 μIU/ml (0.35– 5.5), T_3 47.5 pg/ml (60–181), T_4 1.0 ng/ml (4.5–12.6), through radioimmunoassay, and FSH 6.78 mIU/ml (0.3–2.0), LH < 0.07 mIU/ml (0.1–6.0) and prolactin 185.8 ng/ml (2.8–29.2), through electrochemiluminescence immunoassay. Her radiological investigations revealed a bone age of 7 years (Greulich and Pyle's atlas). Ultrasonography of the pelvis showed a uterine size of 5.4 × 3.2 × 3.6 cm with enlarged multicystic ovaries (right ovary measuring 7.9 × 4.6 cm and left ovary 4.2 × 3.9 cm; Figure 1). The MRI scan of sella revealed a sellar mass with suprasellar extensions of 1.7 × 1.6 × 1.2 cm size [Figure 2]. The radioiodine nuclear thyroid scan did not reveal any functioning thyroid tissue in the neck or chest. During follow-up, her thyroid functions and serum prolactin normalized at 6 months. Repeat ultrasonography revealed complete regression of ovarian cysts with normal sized ovaries at 1 year.

Discussion

The presence of precocious puberty and enlarged ovaries suggested an estrogen-secreting ovarian tumor in the present case. But the finding of a delayed bone age in the patient with precocious puberty narrowed the differential diagnosis to long-standing hypothyroidism. High circulating levels of TSH along with prepubertal LH levels suggested Van Wyk–Grumbach syndrome.

In girls, the condition usually presents with vaginal bleeding, and uncommonly with breast development or galactorrhea. Despite an early stage of puberty, there is lack of pubic hair. Boys have macroorchidism without significant signs of virilization. The salient diagnostic features include long-standing hypothyroidism, [2,3] high levels of TSH,[4] isosexual precocity with lack of public and axillary hair growth, and delayed bone age.[4] The precocious puberty is always isosexual and incomplete in patients of VWGS.[4]

The most common cause of hypothyroidism in these patients is autoimmune thyroditis.[5] Sella turcica enlargement may be seen at times and it has been attributed to thyrotroph hyperplasia. Thus, VWGS can be diagnosed nonoperatively, by the recognition of the salient clinical features and appropriate confirmatory endocrine laboratory tests.[6]

The exact mechanism of the development of precocious puberty in VWGS remains speculative. Van Wyk and Grumbach postulated a lack of specificity in the feedback mechanism leading to an overproduction of multiple hormones.[1] The serum gonadotropin levels in these patients are relatively low for their degree of gonadal stimulation. Immunological activity is present but these gonadotropins are biologically inactive in an *in vitro* assay.[7] Thus, elevated gonadotropins alone cannot completely explain the gonadal stimulation seen in severe juvenile hypothyroidism.

TSH levels are consistently elevated in such patients and the tendency to manifest sexual precocity may be directly related to the severity of TSH elevation. High circulating levels of TSH acting directly on FSH receptors may be the actual mediator of precocity.[7] Using recombinant tools, it has been shown that human TSH can interact with the human FSH receptor to stimulate the adenylyl cyclase

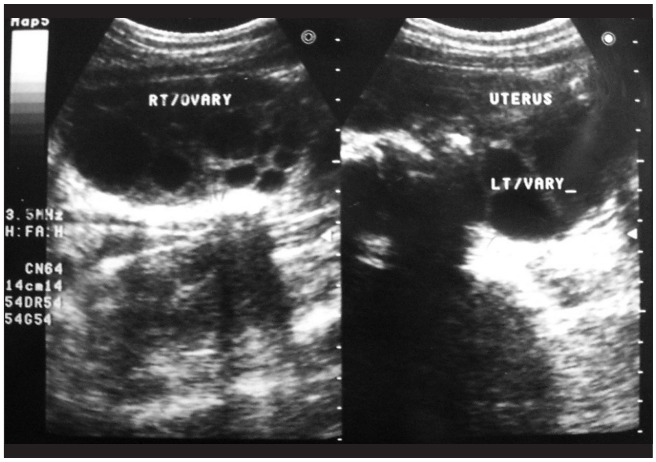

Figure 1: USG showing enlarged and multicystic ovaries

Figure 2: MRI of the sella showing diffusely enlarged pituitary gland

activity. Human recombinant TSH at a dose about 1000-fold greater than hFSH evoked a dose-dependent cyclic AMP response in Chinese hamster ovary (COS-7) cells transfected with the human FSH receptor[7] thus suggesting that relatively low FSH-like activity of TSH can be clinically significant at very high concentrations of TSH present in severe primary hypothyroidism.

A direct effect of severe hypothyroidism on the prepubertal testis, which leads to over proliferation of Sertoli cells is responsible for macroorchidism in males.[8] In females, the multicystic ovaries may result from elevated levels of circulating gonadotropins acting on it. It is also possible that increased sensitivity of the ovaries to the circulating gonadotropins could result from the hypothyroid state directly or via increased prolactin.[9] However, ovarian enlargement may be secondary to a myxedematous infiltration.[10] Our patient also had multicystic ovaries with normal to low gonadotropins, suggesting that the increased sensitivity of ovaries to gonadotropins may be responsible for it. Enlarged pituitary was probably because of thyrotroph hyperplasia.

In patients with isosexual pseudo precocity, the presence of palpable adnexal mass would suggest ovarian tumors but in all such cases, the bone age is advanced. Hence, the presence of a delayed bone age in patients with precocious puberty is an important clue for the diagnosis of VWGS. Although there is little consensus regarding the precise etiopathogenesis of the disorder, the treatment approach is clear. All symptoms subside with thyroxine replacement, the endocrine abnormalities resolve, and even the ovarian cysts decrease in size or altogether disappear, as also in the present case during follow-up.[11]

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